Updated Efficacy Data – GARDASIL®

Eliav Barr
Program Head
HPV Vaccines
Merck Research Laboratories

Presentation Outline

- Clinical program for GARDASIL®
- Updated prophylactic efficacy
- Updated population impact
  - Disease caused by HPV 6/11/16/18
  - Disease caused by vaccine or non-vaccine HPV types

Presentation Outline

- **Clinical program for GARDASIL®**
- Updated prophylactic efficacy
- Updated population impact
  - Disease caused by HPV 6/11/16/18
  - Disease caused by vaccine or non-vaccine HPV types

Clinical Efficacy Program for GARDASIL® in 20,541 Young Women

Study	N	Study Objectives
005	2391	Efficacy through 4 years (HPV 16 vaccine)
007	552	Efficacy through 3 years (GARDASIL®)
	234	Efficacy through 5 years (GARDASIL®) Demonstration of Immune Memory
013	5442	Efficacy and population impact through 4 years (CIN/Warts)
015	12167	Efficacy and population impact through 4 years (CIN 2/3 or AIS)
015NCR	5500	Long-term population effectiveness

Studies of GARDASIL® in New Populations

Study	N	Data Available	Objectives
019 (24-45 year-old women)	3800	Est-3Q 2007	Prevention of persistent HPV 6/11/16/18 infection and disease (Efficacy bridge to Young-adult Women)
020 (16-26 year-old Men)	3900	Est-3Q 2008	Prevention of HPV 6/11/16/18 genital lesions Prevention of HPV 6/11/16/18 infection
020 (16-26 year-old Men)	3900	Est-3Q 2009	Prevention of HPV 6/11/16/18-related anal precancer
NCI (All Ages)	TBD	Starts in 2007	Solid organ and bone marrow transplant patients
ACTG (All Ages)	TBD	Starts in 2007	Immunogenicity in HIV-positive men and women
PATH (Vietnam, Peru, India)	VAR	2008- 2010	Alternative dosing regimens; Vaccine uptake

Est – Estimated (analyses are case-driven)

Presentation Outline

- Clinical program for GARDASIL®
- **Updated prophylactic efficacy**
- Updated population impact
  - Disease caused by HPV 6/11/16/18
  - Disease caused by vaccine or non-vaccine HPV types

Average Duration of Follow-up (Protocols 007, 013, 015)

Population	Start of Efficacy Phase	Original Licensure Database	Current Database
Per Protocol (Naïve to relevant HPV type)	Month 7	1.5 Years	2.4 years
RMITT-2 (Naïve to 14 HPV types)	Day 31	--	2.9 Years
MITT-3 (Infected + Uninfected)	Day 31	2.0 Years	2.8 Years

HPV 16/18-Related Cervical, Vulvar, Vaginal Cancer Efficacy (Via Surrogates)

Per-Protocol Efficacy Population - Protocols 007, 013, 015

HPV 16/18-Related	Analysis	GARDASIL®	Placebo	% Efficacy	95% CI
CIN 2/3 or AIS	Licensure (2005)	0	41	100	91, 100
	Update	1	73	99	92, 100
VIN 2/3 or VaIN 2/3	Licensure (2005)	0	10	100	56, 100
	Update	0	15	100	72, 100

Case of HPV 16-Related CIN 3 in Subject Who Received GARDASIL®

HPV	Day 1		Month 7		Month 13.5		Month 32.5		Month 33.6				
	Swab	Swab	Swab	Swab	Biopsy	ECC	Biopsy	ECC	Biopsy	LEEP 1	LEEP 2	LEEP 3	LEEP 4
52	+	+	NT	NT	-	-	+	-	+	+	+	+	+
16	-	-	-	-	-	-	+	-	-	-	-	-	-

Path Panel Diagnosis = CIN 3

- This case is likely contamination (cannot rule out true endpoint)
- No cases with similar pattern observed in any placebo subjects in P015)
- Anti-HPV levels not tested (not in consistency lot substudy of P015)

HPV 6/11/16/18-Related Cervical, Vulvar, and Vaginal Disease

Per-Protocol Efficacy Population - Protocols 007, 013, 015

HPV 6/11/16/18-Related	Analysis	GARDASIL®	Placebo	% Efficacy	95% CI
CIN (any Grade) or AIS	Licensure (2005)	4	83	95	87, 99
	Update	6†	148	96	91, 99
Vulvar and Vaginal Lesions (incl. Genital Warts)	Licensure (2005)	1	113	99	95, 100
	Update	2 †	189	99	96, 100

† New cases:

- HPV 16/52 CIN 3 as described previously
- HPV 18/56 CIN 1 (prevalent, persistent HPV 56 infection, HPV 56-related CIN 1; single time detection of HPV 18)
- HPV 6/59 genital wart

Conclusions – Prophylactic Efficacy

- Prophylactic administration of GARDASIL® is highly effective in reducing the incidence of:
  - HPV 16/18-related cervical, vulvar, and vaginal cancer
  - HPV 6/11/16/18-related CIN (or AIS)
  - HPV 6/11/16/18-related external genital lesions
- Previously presented data
  - High efficacy maintained through Year 5
  - Long-lived immune memory

Presentation Outline

- Clinical program for GARDASIL®
- Updated prophylactic efficacy
- **Updated population impact**
  - **Disease caused by HPV 6/11/16/18**
  - **Disease caused by vaccine or non-vaccine HPV types**

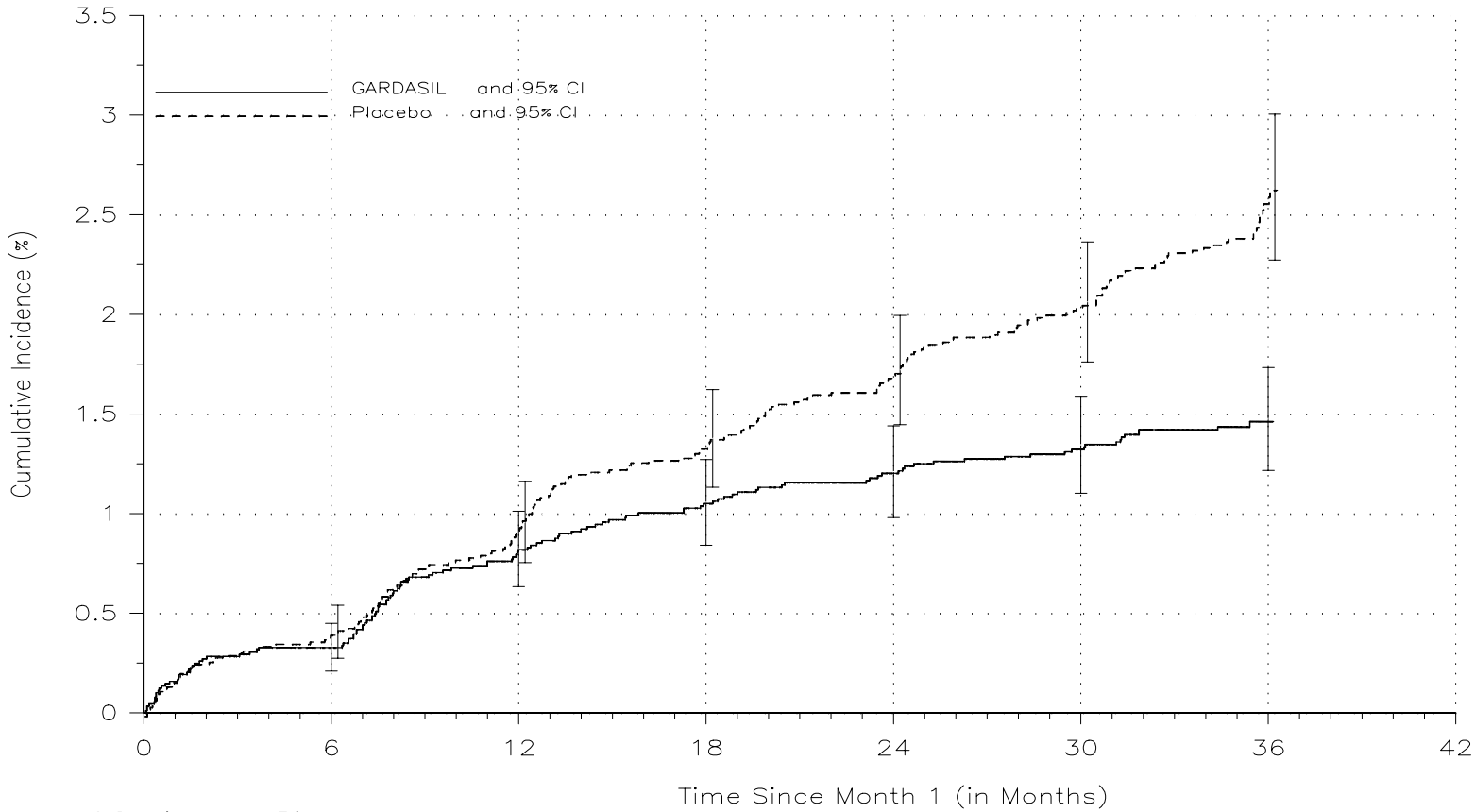
HPV 16/18-Related Cervical, Vulvar, Vaginal Cancer Efficacy (Via Surrogates)

All Subjects, Including HPV-infected Women -Prot 007, 013, 015

HPV 16/18-Related	Analysis	GARDASIL®	Placebo	% Efficacy	95% CI
CIN 2/3 or AIS	Licensure (2005)	117	178	34	16, 48
	Update	137	232	41	27, 53
VIN 2/3 or VaIN 2/3	Licensure (2005)	8	26	69	30, 88
	Update	9	31	71	37, 88

Time to HPV 16/18-Related CIN 2/3 or AIS

All Subjects, Including HPV-infected Women -Prot 007, 013, 015



Number of Subjects at Risk

GARDASIL	8,817	8,728	8,537	8,419	8,154	7,934	2,544
Placebo	8,847	8,750	8,545	8,398	8,139	7,887	2,575

Graphs truncated at M36 (few subjects with follow-up at M42)

HPV 6/11/16/18-Related Cervical, Vulvar, and Vaginal Disease

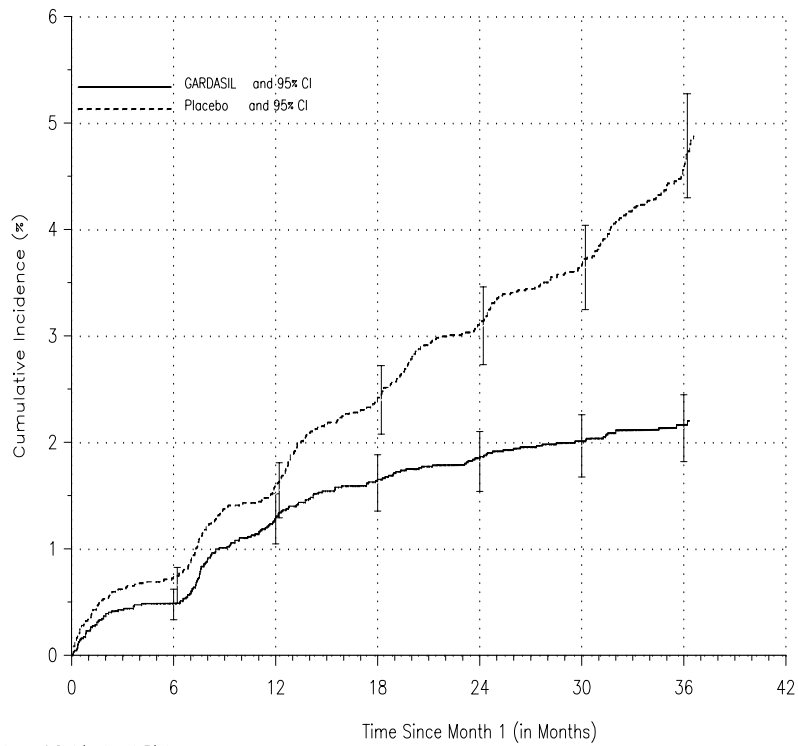
All Subjects, Including HPV-infected Women -Prot 007, 013, 015

HPV 6/11/16/18-Related	Analysis	GARDASIL®	Placebo	% Efficacy	95% CI
CIN (any Grade) or AIS	Licensure (2005)	170	317	46	35, 56
	Update	192	414	54	45, 61
Vulvar and Vaginal Lesions (incl. Genital Warts)	Licensure (2005)	68	229	70	61, 78
	Update	72	319	78	71, 83

Time to HPV 6/11/16/18-Related Cervical, Vulvar, and Vaginal Disease

All Subjects, Including HPV-infected Women -Prot 007, 013, 015

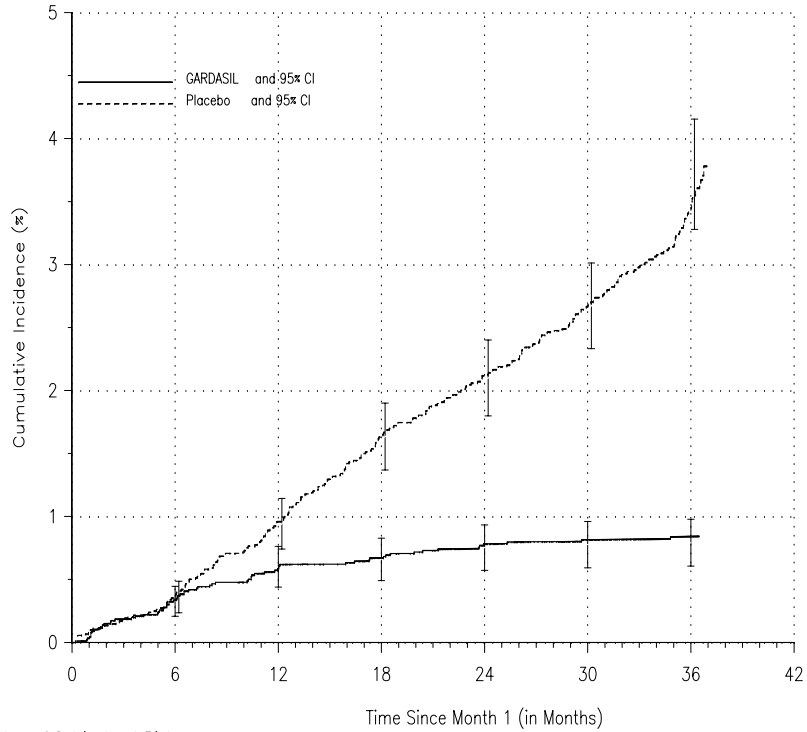
CIN (any grade) or AIS



Number of Subjects at Risk

GARDASIL	8,817	8,718	8,507	8,386	8,126	7,908	2,535
Placebo	8,847	8,736	8,506	8,330	8,048	7,794	2,518

External Genital Lesions



Number of Subjects at Risk

GARDASIL	8,954	8,767	8,621	8,561	8,378	8,225	2,447
Placebo	8,964	8,792	8,612	8,496	8,291	8,082	2,417

Graphs truncated at M36 (few subjects with follow-up at M42)

Population Definitions (Protocol 013 or 015)

Population	Description	Application	Relevance
RMITT-2	At Day 1, naïve to 14 HPV types and Pap test negative	Key analysis of Population Impact	HPV-naïve adolescents and young women
MITT-3	All subjects with efficacy follow-up	Supportive analyses	General population of young women (including HPV- infected at vaccination onset)

RMITT-2 is not completely HPV-naïve (testing covers 12/17 cancer causing HPV types)

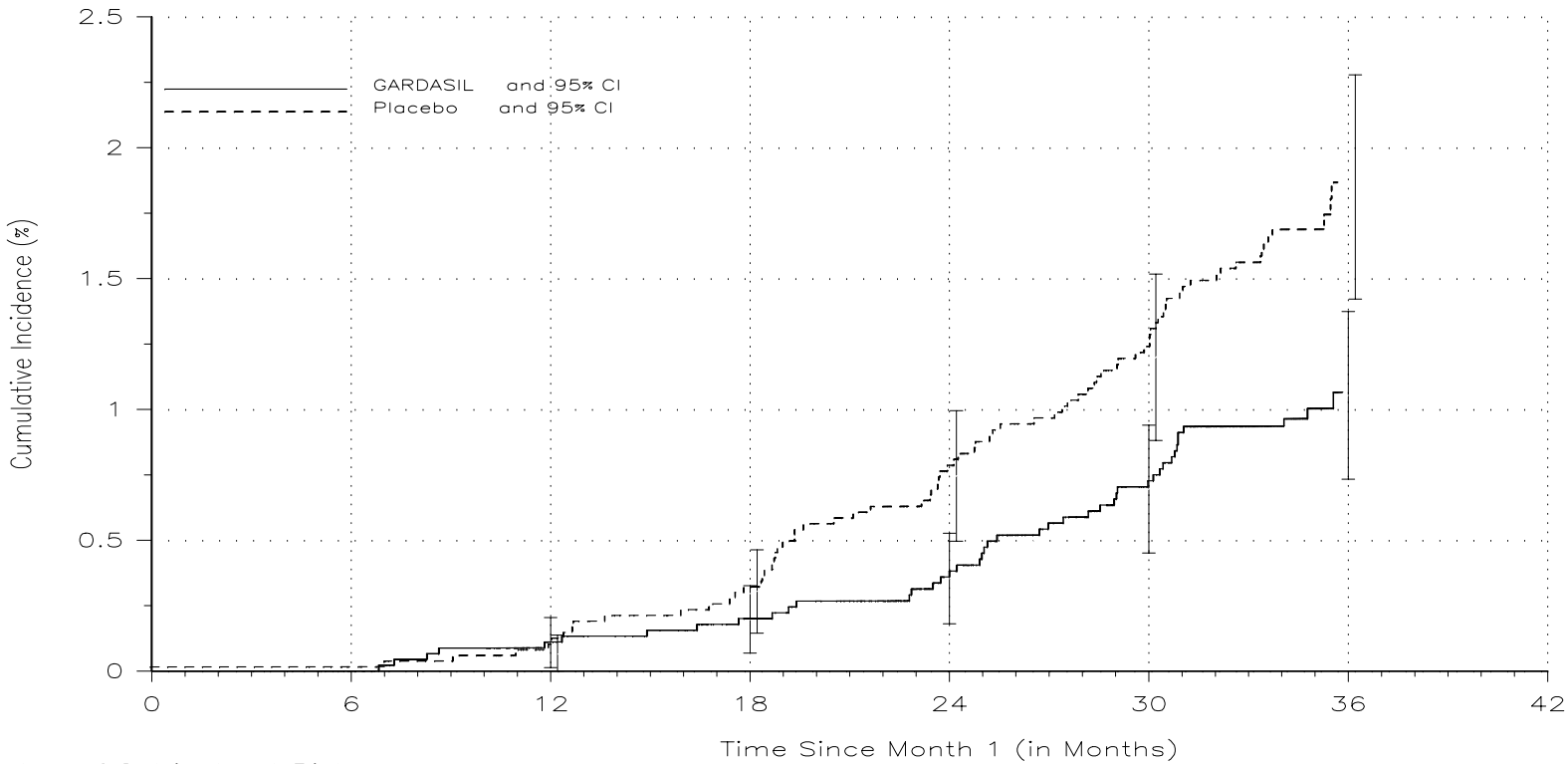
Overall Population Impact at Year 3 Phase III Program

Endpoint	Analysis Population	Subjects With an Endpoint		% Reduction (95% CI)
		GARDASIL™	Placebo	
CIN 2/3 or AIS	RMITT-2	52	97	46 (24, 62)
	Any HPV Infection at Day 1†	309	320	--
	MITT-3	361	417	14 (0.1, 25)
VIN 2/3 or VaIN 2/3	RMITT-2	6	25	76 (40, 92)
	Any HPV Infection at Day 1†	21	27	--
	MITT-3	27	52	48 (16, 69)
CIN or AIS	RMITT-2	191	272	30 (15, 42)
	HPV Infection at Day 1†	624	695	--
	MITT-3	815	967	16 (8, 24)
EGL	RMITT-2	49	189	74 (64, 82)
	Any HPV Infection at Day 1†	164	226	--
	MITT-3	213	415	49 (40, 57)

† At Day 1: PCR(+) to HPV 6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and/or 59; and/or Pap test ≥ASC-US; and/or anti-HPV 6, 11, 16, and/or 18 seropositive.

Time to CIN 2/3 or AIS (Caused by Vaccine or Non-Vaccine Types)

RMITT-2 (Phase III) Population
Approximates HPV-Naïve Girls/Women



Number of Subjects at Risk

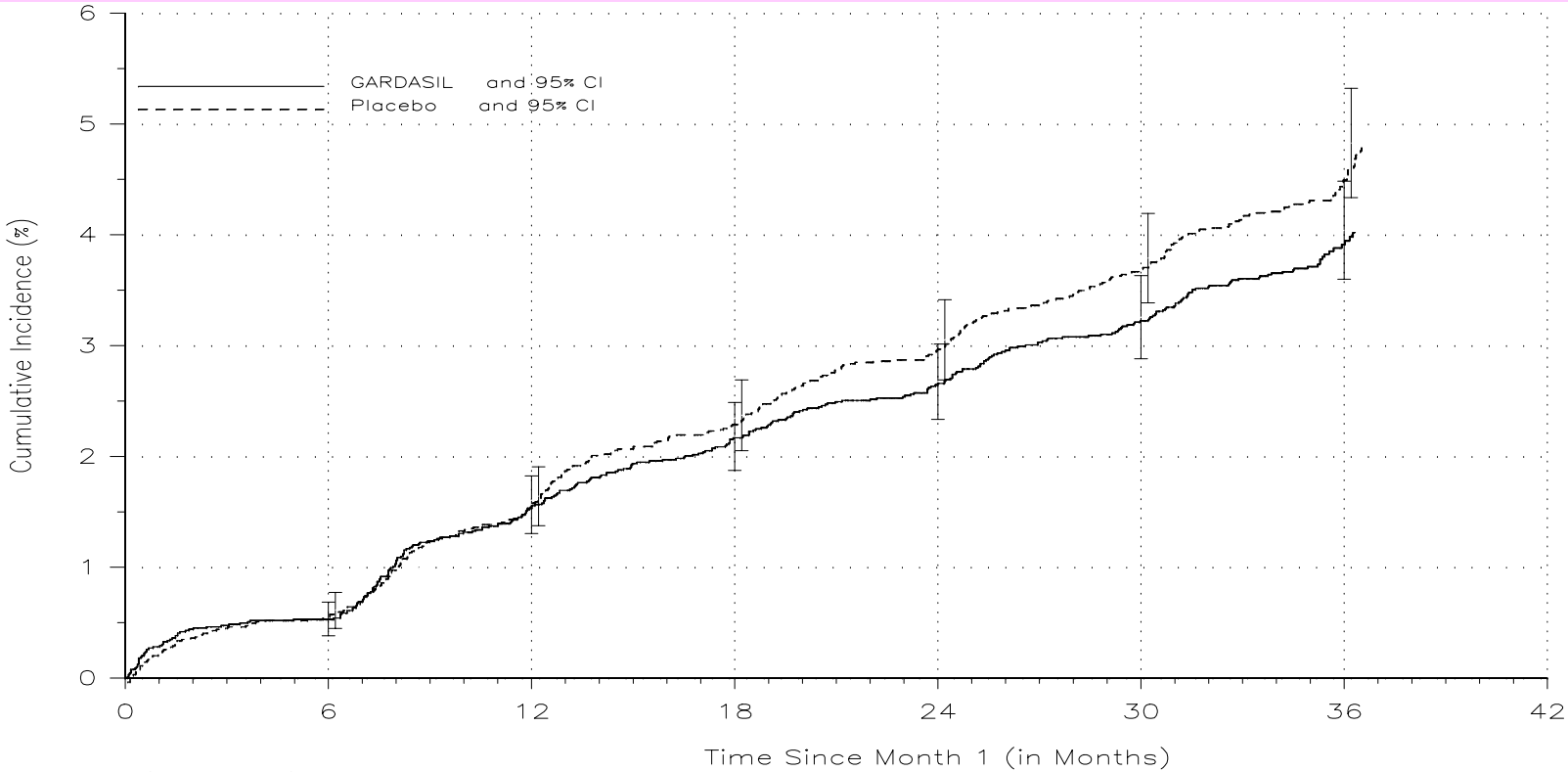
GARDASIL	4,616	4,606	4,541	4,507	4,404	4,317	1,410
Placebo	4,675	4,666	4,599	4,555	4,425	4,303	1,457

Graphs truncated at M36 (few subjects with follow-up at M42)

Time to CIN 2/3 or AIS (Caused by Vaccine or Non-Vaccine Types)

MITT-3

Approximates General Population (Including Women With HPV Infection at Day 1)



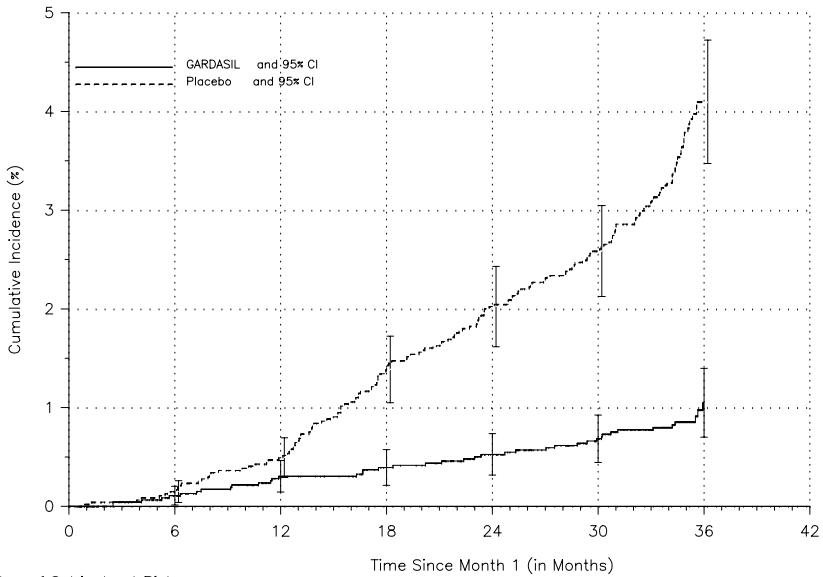
Number of Subjects at Risk

GARDASIL	8,817	8,723	8,508	8,377	8,114	7,895	2,516
Placebo	8,847	8,741	8,518	8,369	8,103	7,842	2,551

Graphs truncated at M36 (few subjects with follow-up at M42)

Time to External Genital Lesions

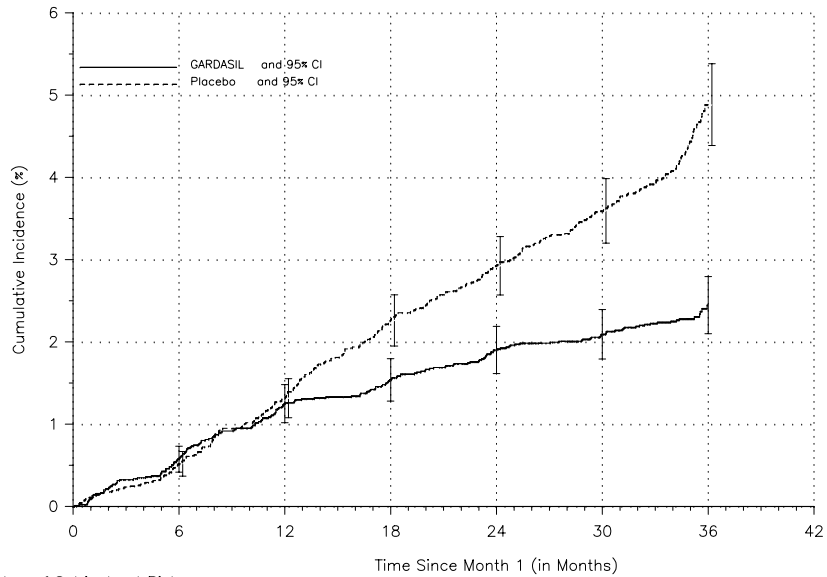
RMITT-2
Approximates
HPV-Naïve Girls/Women



Number of Subjects at Risk

GARDASIL	4,688	4,610	4,535	4,500	4,421	4,347	1,339
Placebo	4,732	4,665	4,583	4,513	4,402	4,290	1,326

MITT-3
Approximates
General Population of Women



Number of Subjects at Risk

GARDASIL	8,954	8,745	8,564	8,485	8,282	8,115	2,406
Placebo	8,964	8,778	8,579	8,441	8,221	8,005	2,377

Graphs truncated at M36 (few subjects with follow-up at M42)

Impact of GARDASIL® on Non-Vaccine HPV Types ("Cross-Protection")

- Protocol 013/015 combined clinical disease analysis
  - Encouraging preliminary results
  - Cervical, vulvar, and vaginal disease impact
- Protocol 013 substudy – persistent infection efficacy
  - Needed to confirm findings of combined clinical disease analysis
  - Results available in near term
- Public presentations in 2007

Conclusions
Population Impact

- In girls and women, administration of GARDASIL® reduces overall risk of
  - cervical, vulvar, and vaginal cancer
  - CIN
  - genital warts
- Reductions in Pap test abnormalities, cervical procedures observed
- Benefits becomes more apparent over time
- Preliminary cross-protection efficacy data encouraging – definitive evaluation ongoing